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ORIGINAL ARTICLE

Low levels of insulin-like growth factor 1 (IGF-1) and morbidity in preterm newborns

Niveles séricos bajos de factor de crecimiento insulínico tipo 1 (IGF-1) y morbilidad en el recién nacido prematuros

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What do we know about the subject matter of this study?

Insulin-like growth factor 1 (IGF-1) is the main mediator of fetal growth. In preterm infants < 1500 grams or < 32 weeks at birth, an association has been observed between low levels of this factor and some morbidities such as bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, and impaired brain growth and development.

What does this study contribute to what is already known?

We present the first study to measure serum levels of IGF-1 in very low birth weight preterm infants in Chile. The association between low IGF-1 levels and bronchopulmonary dysplasia, late neonatal sepsis, and patent ductus arteriosus is demonstrated. These results provide the basis for multicenter studies to determine the association of IGF-1 with other neonatal morbidities in our country.

Abstract

Insulin-like growth factor 1 (IGF-1) is the main mediator of fetal growth. An association has been described between low levels of IGF-1 and the development of some morbidities such as bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) in newborns weighing less than 1500 grams or less than 32 weeks at birth. **Objective:** To determine the association between serum levels of IGF-1 and morbidity in premature infants. **Patients and Method:** prospective observational study in 40 newborns. Serum levels of IGF-1 were measured at 24 hours and 15, 30, and 45 postnatal days. Pathologies such as BPD, ROP, intraventricular hemorrhage (IVH), and other neonatal morbidities and their association with serum IGF-1 levels were identified. **Results:** The mean gestational age and birth weight of the newborns were 28.7 weeks (range 24-32) and 1248 grams (range 680-2100), respectively. There was an association between low IGF-1 levels and BPD at 15 and 30 days (p = 0.035 and 0.018); with late sepsis at 15 and 30 days (p = 0.038 and 0.010), and with hemodynamically significant patent ductus arteriosus (hs-PDA) at 30 days (p = 0.03). No association of low IGF-1 levels with other pathologies was found**. Conclusion:** There was an association between low postnatal IGF-1 levels and BPD, late sepsis, and hs-PDA. New prospective studies are required to corroborate these results and the association between low IGF-1 levels and other neonatal morbidities.

Keywords:
Insulin-Like Growth Factor 1;
IGF-1;
Newborn;
Prematurity;
Retinopathy of Prematurity;
Bronchopulmonary Dysplasia

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Introduction

Insulin-like growth factor 1 (IGF-1) is a small peptide composed of 70 amino acids with a molecular weight of 70 Daltons and a molecular structure similar to proinsulin[1]. In plasma, approximately 99% of IGF-1 forms complexes with one of its 6 binding proteins (IGFBP), with IGFBP-3 being the most abundant (80%)[1]. Liver is the main producer, and its receptor is a specific tyrosine kinase, which is present in various tissues, including the nervous system, endothelial cells, skeletal muscle, lungs, bones, cartilage, kidneys, liver, skin, and hematopoietic stem cells[1].

IGF-1 regulates cell differentiation and growth through modulation of DNA biosynthesis and is one of the activators of the protein kinase B signaling pathway that stimulates cell proliferation[2]. In addition, it has insulin-like effects and is involved in glucose and lipid metabolism[3].

During fetal life, serum IGF-1 levels are regulated by the supply of nutrients from the mother to the fetus, which continuously receives a diet high in carbohydrates and amino acids[3]. Its action is mediated by the glucose-insulin axis, which allows a rapid response to nutritional fluctuations[3]. IGF-1 production begins in the first trimester of pregnancy, increasing significantly during the third trimester, when accelerated fetal growth occurs[2,3]. Fetal IGF-1 concentrations have been evaluated in samples obtained by cordocentesis between 20 and 42 weeks, where it can be established a linear relationship between serum levels and birth weight and gestational age[4].

In preterm infants, especially in very low birth weight (VLBW) infants or those weighing < 1,500 grams, there is a rapid decrease in serum IGF-1 concentrations, which reach an average of 10 ng/ml after birth, unlike what occurs in the fetus with gestational age between 23 and 30 weeks postmenstrual that maintain levels over 50 ng/ml[3,5]. This decrease is multifactorial and is related to the adequate availability of nutrients, insulin action, hypoxia episodes, and the presence of proinflammatory cytokines[3,5,6].

For VLBW infants, growth in the early neonatal period is critical, and adequate weight-length development has been associated with improved short- and long-term outcomes[7]. Serum IGF-1 concentrations correlate positively with weight, length, head circumference, and ponderal index[8,9].

Several studies have described an association between persistently low serum IGF-1 levels and the development of some morbidities such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), impaired brain development, and impaired growth in VLBW newborns[9,10].

Hypothesis: Low IGF-1 levels are related to some morbidities, such as BPD and ROP.

The objective of this study was to determine the association between serum IGF-1 levels and some morbidities in VLBW infants.

Patients and Method

Prospective observational study in 40 very low birth weight preterm infants (< 1,500 grams and/or < 32 weeks of gestational age), born at the *Hospital Guillermo Grant Benavente* (HGGB) of Concepción and hospitalized in its neonatal ICU of the Neonatology Service, in a 10-month-period from September 1, 2020, to June 30, 2021.

Patients under 24 weeks of gestational age and/or under 500 grams at birth, neonates with major malformations and/or chromosomopathies, and patients transferred to another healthcare center or who died before 30 days of life, in whom it was not possible to complete the sample collection, were excluded.

Preterm infants who met the inclusion criteria underwent measurement of serum IGF-1 levels on the first day of life and subsequently at 15, 30, and 45 days. For each test, 0.8 to 1.0 ml of venous blood was collected, centrifuged, and stored at -20°C in the central laboratory of the HGGB, to be processed once a week with the enzyme immunoassay method (Immulite® 2000 IGF-1, Siemens Healthcare Diagnostics Ltd.).

In all the preterm infants in the study, an active search for pathologies associated with prematurity was performed according to the protocol of the Neonatology Service of the HGGB, through the following interventions: echocardiography between 24 and 72 hours postnatal for diagnosis of hemodynamically significant patent ductus arteriosus (hs-PDA), according to echocardiographic criteria[11], transfontanellar ultrasound during the first 72 hours postnatal and later at 7, 14 and 30 days, looking for lesions such as IVH and periventricular leukomalacia (PVL); serial fundus examination through indirect ophthalmoscopy from 4 weeks of chronological age, for detection and follow-up of ROP.

A record file was prepared to register the data of each patient enrolled from birth to 45 days of life. Demographic characteristics, indicated treatment, and diagnosed morbidities were recorded, such as BPD according to the 2001 criteria of the National Institute of Health (NICHD)[12]; ROP according to the international classification[13]; late sepsis, defined by the deterioration of clinical status and positive blood culture; confirmed NEC (Bell's stage ≥ II); IVH according to Papile's classification[14], and PVL according to Linda de Vries' classification[15].

The study was approved by the Scientific Ethics Committee of the Concepción Health Service and all patients' parents signed informed consent.

For the description of qualitative variables, proportions and frequencies were used; quantitative variables were analyzed with their mean and standard deviation (SD) or median and range according to the nature of the variable. The Kruskal-Wallis test was used to compare the mean IGF-1 values at the different measurement times, and the differences between each time were adjusted by Bonferroni. To evaluate the association between each morbidity and IGF-1 values at 24 hours, Mann Whitney U analysis was used (non-normal distribution) and for the analysis of 15, 30, and 45 days, the T-Student test was used. A $p < 0.05$ was considered significant. SPSS statistical software version 28.0 (IBM) was used for data analysis.

Results

During the study period, 78 preterm infants less than 32 weeks and/or less than 1,500 g at birth were eligible, 40 of them met the inclusion criteria (figure 1).

Mean gestational age and birth weight ± SD were 28.7 ± 2.0 weeks (range 24 - 32) and 1 248 ± 308 g (range 680 - 2 100), respectively. There was a slight predominance of male gender (22/40; 55%) (table 1).

Among the treatments administered to the mother, 95% of them received antenatal corticosteroids and 52.5% received antibiotics before delivery.

The median and range of invasive mechanical ventilation and non-invasive ventilation were 1 (0-135) and 6 (0-83) days, respectively, and the median and range of oxygen therapy were 12 days (1-180) (table 1).

Table 2 shows the morbidities found in the VLBW infants, highlighting hs-PDA in 62.5%, BPD in 40%, and ROP in 30%. Only 1 newborn who met the inclusion criteria died before hospital discharge due to NEC that progressed to Bell's stage III B, at 65 days of life.

In relation to serum IGF-1 levels, a progressive increase in its values was observed as postnatal age increased, with mean levels ± SD of 16.5 ± 4.0 ng/ml at the end of the first day of life, 27.8 ± 11.5 ng/ml at 15 days, 35.7 ± 17.6 ng/ml at 30 days, and 37.2 ± 14.4 ng/ml at 45 days. The increase in IGF-1 between 24 hours and 15 days of life was statistically significant ($p < 0.001$), a situation that was not observed in subsequent measurements (figure 2).

Table 3 shows the association between the most frequent morbidities in VLBW infants and IGF-1 levels at 24 hours and at 15, 30, and 45 days of life. Lower IGF-1 levels were observed in patients with BPD at 15 and 30 days ($p = 0.035$ and 0.018). These neonates also had lower IGF-1 levels at 45 days of life, but without statistical significance ($p = 0.078$).

Preterm infants with late sepsis had lower IGF-1 levels at 15 and 30 days ($p = 0.038$ and 0.010) compared with those who did not develop sepsis. Neonates with hs-PDA also showed lower IGF-1 levels at 30 days ($p = 0.03$).

No significant association was found between low IGF-1 levels with ROP, IVH, PVL, and NEC in any of the periods.

Discussion

In this prospective observational study, we found persistently low serum IGF-1 levels in the first weeks of life in newborns < 1,500 grams and/or < 32 weeks of gestational age. However, these values increase with increasing postnatal age, reaching a mean of 37.2 ng/ml at 45 days of life, which is below IGF-1 levels measured in cord blood between 24 - 32 weeks of postmenstrual age (average 58 ng/ml), being higher than 100 ng/ml over 33 weeks[4]. Lineham et al.[16] describe low serum IGF-1 concentrations on the first day of life in both preterm and term neonates. In preterm newborns younger than 33 weeks, a slow increase in these levels is observed until approximately 44 weeks of postmenstrual age; in contrast, in term infants, the increase in IGF-1 is rapid and occurs between 10-15 days of life[16]. It has been shown that persistently low levels of IGF-1 between 30-33 weeks postmenstrual age are associated with the development of ROP and other severe postnatal morbidities, such as BPD, IVH, and NEC[10,17,18].

In this study, we observed that neonates with BPD had significantly lower IGF-1 levels at 15 and 30 days of life, a decrease that remained at 45 days, but without

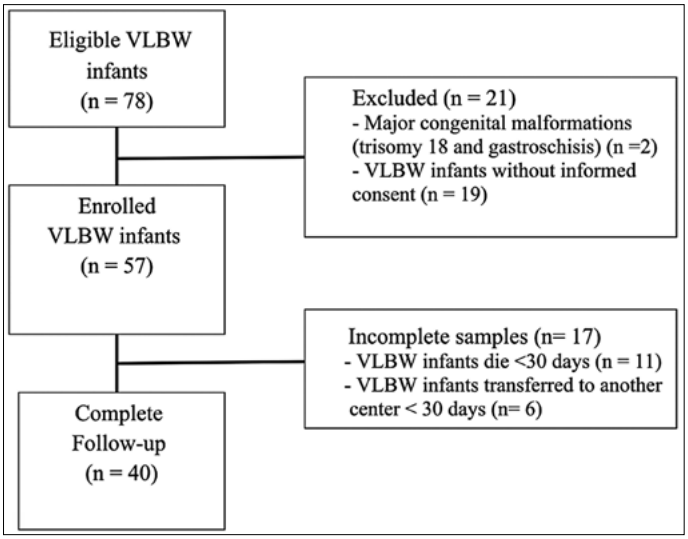

Figure 1. Study flow chart. VLBW: very low birth wight; NBs: newborns.

Table 1. Demographic characteristics perinatal history and treatment received

Characteristics	N = 40
Male. n (%)	22 (55.0)
Gestational age. weeks (mean ± SD)	28.7 ± 2.0
Cesarean delivery. n (%)	27 (67.5)
Birth weight. g (mean ± SD)	1.248 ± 308
Birth height. cm (mean ± SD)	37.9 ± 3.4
Head circumference. cm (mean ± SD)	26.9 ± 2.2
SGA. n (%)	6 (15.0)
Apgar score 1 min. median (range)	7 (1-9)
Apgar score 5 min. median (range)	8 (4-9)
Antenatal corticosteroids. n (%)	38 (95.0)
Antenatal antibiotics. n (%)	21 (52.5)
PROM>18 hours. n (%)	12 (30.0)
Treatments	
Surfactant. n (%)	28 (70.0)
Days of invasive mechanical ventilation. median (range)	1 (0-135)
Days of non-invasive ventilation. median (range)	6 (0-83)
Oxygen days. median (range)	12 (1-180)
Oxygen at 28 days. n (%)	17 (42.5)
Postnatal antibiotics days. median (range)	3 (0-41)
Vasoactive drugs days. median (range)	0 (0-14)
Parental nutrition days. median (range)	7 (0-27)

SD: Standard deviation; SGA = small for gestational age; PROM: premature rupture of membranes.

statistical significance.

In relation to serum IGF-1 levels and lung development, it has been demonstrated in animal models that IGF-1 is essential during prenatal lung growth and organogenesis[19]. The cells responsible for local IGF-1 synthesis in the lung are type II pneumocytes, alveolar macrophages, and mesenchymal stem cells[19,20].

Preterm newborns have incomplete lung development and, in extremely preterm infants, their association with different postnatal noxae that affect the lung can lead to BPD, which is the main respiratory sequela of VLBW infants which has increased in recent years, despite important advances in perinatal and neonatal care and extensive postnatal research[21]. Our results are consistent with the findings of Löfqvist et al.[17], who report lower serum IGF-1 concentrations between 3-21

Table 2. Morbidity observed in 40 preterm newborns

Retinopathy of prematurity. n (%)	12 (30)
Bronchopulmonary displasia. n (%)	16 (40)
Intraventricular hemorrhage. n (%)	9 (22.5)
Periventricular leukomalacia. n (%)	8 (20)
Necrotizing enterocolitis. n (%)	4 (10)
Hs-PDA. n (%)	25 (62.5)
Early sepsis. n (%)	4 (10)
Late sepsis. n (%)	12 (30)
Death before discharge. n (%)	1 (2.5)

hs-PDA: hemodynamically significant patent ductus arterio<sus

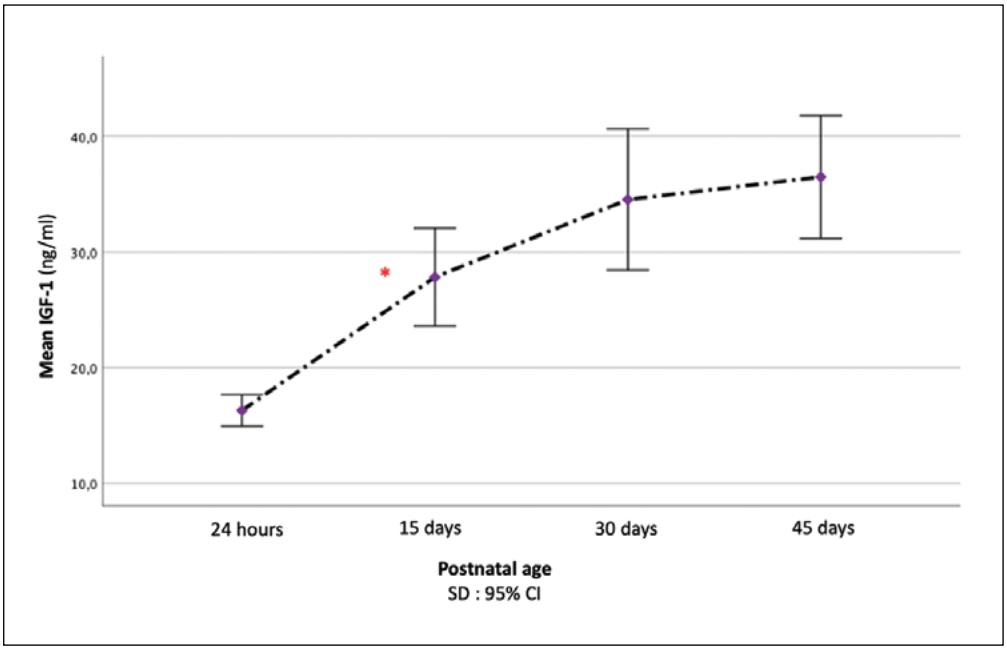

Figure 2. Mean IGF-1 levels ± SD in different postnatal periods. IGF-1: insulin-like growth factor 1 ; SD: standard deviation
*p <.001. significant increase in IGF-1 between 24 hrs and 15 days.

Table 3. Association between neonatal morbidities and serum IGF-1 levels (ng/ml) at 24 hours, 15, 30 and 45 days of life

	IGF-1 24 hours			IGF-1 15 days			IGF-1 30 days			IGF-1 45 days		
Morbidity	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
	Mean (SD)			Mean (SD)			Mean (SD)			Mean (SD)		
ROP	15.8 (2.1)	16.9 (4.6)	0.361	24.2 (12.5)	29.3 (11.1)	0.152	28.6 (19.7)	38.4 (16.4)	0.106	32.4 (13.6)	39.1 (14.6)	0.121
DBP	15.8 (1.8)	16.9 (4.8)	0.654	23.3 (12.0)	31.1 (10.3)	0.035	27.8 (13.6)	40.2 (18.3)	0.018	32.3 (15.3)	40.2 (13.3)	0.078
HIV	18.4 (8.0)	16.0 (2.1)	0.895	27.4 (15.4)	27.9 (10.8)	0.467	34.3 (12.3)	36.0 (18.8)	0.389	36.0 (11.9)	37.4 (15.0)	0.410
LPV	18.2 (7.5)	16.0 (2.1)	0.545	30.9 (14.4)	27.2 (11.1)	0.305	31.2 (13.3)	37.2 (18.8)	0.168	31.9 (11.0)	38.4 (15.0)	0.127
ECN	15.0 (0.01)	16.6 (4.1)	0.363	25.7 (17.0)	28.1 (10.9)	0.400	26.7 (17.0)	36.6 (17.7)	0.211	40.9 (20.5)	36.6 (13.7)	0.357
hs-PDA	15.7 (7.2)	12.6 (9.0)	0.523	26.8 (12.0)	29.0 (11.2)	0.298	31.5 (19.0)	42.2 (13.4)	0.033	35.4 (14.7)	40.5 (13.8)	0.174
LOS	15.7 (1.8)	16.9 (4.7)	0.373	22.5 (12.4)	30.7 (10.2)	0.038	26.1 (12.7)	39.9 (18.0)	0.010	32.7 (16.3)	39.3 (13.3)	0.141

ROP: retinopathy of prematurity; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; PVL: Periventricular leukomalacia; NEC: necrotizing enterocolitis; hs-PDA: hemodynamically significant patent ductus arteriosus; LOS: Late onset sepsis; SD: standard deviation. $p < 0.05$.

days postnatal and 30-33 weeks postmenstrual in neonates who developed BPD, regardless of gestational age and birth weight.

The analysis of this study showed that in the total group of patients with ROP, there was only a tendency to have lower IGF-1 levels.

Retinopathy of prematurity is a vasoproliferative disorder of the immature retina that mainly affects VLBW infants, being the main cause of infant blindness in developing countries; also, an association has been demonstrated between the development of ROP and IGF-1 levels[18,22]. In the pathogenesis of ROP, it has been observed that in phase I, there are usually low levels of IGF-1, therefore, the neonate must maintain normal levels of this factor to avoid the development of this pathology[23]. Several studies have related the presence of low IGF-1 levels at 3 weeks postnatal and between 30-33 weeks postmenstrual with ROP, especially in its most severe forms[10,25,26].

Based on these findings, algorithms have been developed to predict the development of retinopathy from gestational age, birth weight, serum IGF-1 levels, and postnatal weight gain[27,28]. In this study, we found no association between ROP and low IGF-1 levels, which could be due to the low incidence of severe retinopathy (N = 3), being the most closely related to low levels of this growth factor. When performing a subanalysis of IGF-1 levels in this group, significantly lower levels were observed; however, since the sample size was very small, we cannot draw any conclusions.

Our study also demonstrated lower IGF-1 levels at 15 and 30 days in patients with late onset sepsis. In neonates with sepsis, it has been shown that proinflammatory cytokine levels are elevated[29]. Clinical trials in pediatric and adult populations with sepsis have demonstrated alteration of the somatotropic axis with increased growth hormone and decreased IGF-1 and IGFBP-3, compared with healthy controls[30,31].

In a study in children with septic shock, IGF-1 was markedly decreased and, at the same time, elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were observed[32]. In a recent trial in VLBW infants, which evaluated levels of proinflammatory cytokines, low levels of IGF-1 were found concomitant with elevated levels of IL-6 between 5 - 8 weeks postnatal[33]. Another study in extremely preterm infants who received continuous infusion of recombinant human IGF-1/IGFBP-3 complex (rhIGF-1/IGFBP-3) showed that low serum IGF-1 levels were preceded by high levels of IL-6 and IGFBP-1[34]. The mechanisms through which proinflammatory cytokines decrease IGF-1 levels are unclear, but it is proposed that this may be related to an increase in vascular IGF-1 clearance. IL-6 and other proinflammatory cytokines have been shown to increase the production of IGFBP-1 and induce proteolysis of IGFBP-3, increasing the proportion of free IGF-1. IGF-1 forms a smaller complex with IGFBP-1, which can leave the vascular compartment[34]. This could explain the low serum IGF-1 levels found in our

children with sepsis.

In this study, an association between hs-PDA and low IGF-1 levels at 30 days of life was also observed. We found no reports on this association in the literature and believe that other factors that may be contributing to the high rate of hs-PDA found and to the persistence of low serum IGF-1 levels in these patients should be reviewed locally.

From the neurological perspective, low IGF-1 concentrations have been associated with reduced head circumference growth[35], increased risk of IVH, and neurodevelopmental impairment in preterm infants[36]. In this study, there was no association between low IGF-1 levels and IVH or PVL. Long-term follow-up would be important to determine the possible association between IGF-1 levels and neurodevelopment in the population.

An association between persistently low IGF-1 levels and increased risk of developing NEC has also been described, but this study did not find this association. At the gastrointestinal level, IGF-1 promotes cell growth, participates in healing, and has anti-inflammatory properties[37]. Animal studies of NEC using a mouse model demonstrated that administration of IGF-1 before the injury resulted in decreased epithelial cell apoptosis and improved survival of the affected rats[37].

Considering the importance of IGF-1 in postnatal development and its association with severe neonatal pathologies, exogenous administration of IGF-1 through the rhIGF-1/IGFBP-3 complex is being evaluated as a treatment for premature patients. Some preclinical models support associations between IGF-1 and complications of prematurity. In mice, the absence of IGF-1 delays normal retinal vascular development[38] and the administration of rhIGF-1 reduces the risk of oxygen-induced retinopathy[39]. In addition, the administration of rhIGF-1 in a hyperoxia-induced BPD model decreases signs of disease in neonatal rats[40].

Phase I and II randomized controlled clinical trials (RCTs) on the pharmacokinetics and safety of rhIGF-1/IGFBP-3 revealed no significant adverse effects[41,42]. A clinical trial on the administration of rhIGF-1/IGFBP-3 from birth to 29+6 weeks postmenstrual age in newborns with gestational age between 23-27 weeks showed no difference in the incidence of ROP. However, a significant reduction in the incidence of severe BPD was demonstrated in this group of neonates (53%). This study also showed a trend towards lower grades 3 and 4 IVH[43]. Another RCT (Identifier: NCT03253263)[44] is currently ongoing to evaluate the efficacy of rhIGF-1/IGFBP-3 in the treatment of BPD in VLBW infants, and it is believed that the results of this study may provide a solid basis for the future treatment of BPD with this growth factor.

One of the strengths of our study is that it is the first to evaluate serum IGF-1 levels in preterm newborns in Chile and lays the foundations for multicenter studies in our country.

Regarding the limitations, the small size of the population analyzed stands out since patient recruitment began during the SARS-CoV-2 pandemic and there were restrictions on visits to neonatal patients, which made it difficult to obtain informed consent and to recruit a larger population of neonates. Also, we initially considered weekly monitoring of IGF-1 concentrations, but given the low birth weight and gestational age of the population analyzed, it was decided to collect only 4 samples together with the tests that are usually requested in premature infants to evaluate nutritional and metabolic status.

Conclusions

This study demonstrates the presence of persistently low serum IGF-1 levels during the first postnatal weeks in preterm infants.

An association was found between low postnatal IGF-1 levels at 15 and 30 days with the development of BPD, at 15 and 30 days in preterm infants with late sepsis, and at 30 days with the presence of hs-PDA. No association was observed between low IGF-1 levels and other neonatal morbidities.

Multicenter studies with a larger number of patients are required to corroborate the association between low serum IGF-1 levels with BPD and to evaluate its association with ROP in the population of VLBW infants in Chile.

Increasing serum IGF-1 levels in VLBW preterm infants by the administration of the rhIGF-1/IGFBP-3 complex could help prevent BPD and other serious neonatal morbidities.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Central Laboratory of the *Hospital Guillermo Grant Benavente* of Concepción.

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